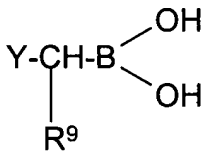
## Claims

This listing of claims will replace all prior versions, and listings, of claims in the application:

**Listing of Claims:**

Claim 1 (original): A salt of a pharmaceutically acceptable multivalent metal and an organoboronic acid inhibitor of thrombin having a neutral thrombin S1-binding moiety linked to a hydrophobic thrombin S2/S3-binding moiety.

Claim 2 (original): A salt of claim 1 wherein the organoboronic acid is of Formula (III):




(III)

wherein

Y comprises a moiety which, together with the fragment $-CH(R^9)-B(OH)_2$, has affinity for the substrate binding site of thrombin; and

$R^9$ is a straight chain alkyl group interrupted by one or more ether linkages and in which the total number of oxygen and carbon atoms is from 3 to 6, or is $-(CH_2)_m-W$ where m is from 2 to 5 and W is –OH or halogen (F, Cl, Br or I).

Claim 3 (original): A salt of claim 2 wherein $R^9$ is an alkoxyalkyl group.

Claim 4 (original): A salt of claim 2 wherein Y comprises an amino acid which binds to the S2 subsite of thrombin and is linked to $-CH(R^9)-B(OH)_2$ by a peptide linkage, the amino acid being N-terminally linked to a moiety which binds the S3 subsite of thrombin.

Claim 5 (original): A salt of claim 4 wherein Y comprises an N-terminally protected dipeptide residue which binds to the S3 and S2 binding sites of thrombin and is linked to –$CH(R^9)$-$B(OH)_2$ by a peptide linkage.

Claim 6 (original): The salt of claim 1 wherein the boronic acid has a Ki for thrombin of about 100 nM or less.

Claim 7 (original): The salt of claim 5 wherein the Y dipeptide is N-terminally protected or N-terminally unprotected, and the peptide linkages in the dipeptide are unsubstituted or independently N-substituted by a $C_1$-$C_{13}$ hydrocarbyl, wherein the $C_1$-$C_{13}$ hydrocarbyl contains no heteratoms or at least one in-chain or in-ring nitrogen, oxygen or sulfur atom, and the $C_1$-$C_{13}$ hydrocarbyl is unsubstituted or substituted by a substituent selected from halo, hydroxy and trifluoromethyl.

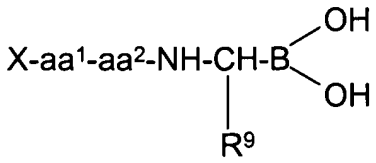
Claim 8 (original): The salt of claim 1 wherein the multivalent metal comprises calcium, magnesium or zinc.

Claim 9 (original): The salt of claim 1 wherein the salt consists essentially of an acid salt in which one B-OH group of formula (I), when trigonally represented, remains protonated.

Claim 10 (original): The salt of claim 7 wherein the salt comprises boronate ions derived from the peptide boronic acid and has a stoichiometry consistent with the boronate ions carrying a single negative charge.

Claim 11 (currently amended): The salt of claim 3 wherein the salt consists essentially of a hemicalcium or hemimagnesium salt of the boronic acid.

Claim 12 (previously presented): The salt of claim 1 wherein the peptide boronic acid is of formula (IV):




(IV)

where:

X is H or an amino-protecting group;

$aa^1$ is an amino acid having a hydrocarbyl side chain containing no more than 20 carbon atoms and comprising at least one cyclic group having up to 13 carbon atoms;

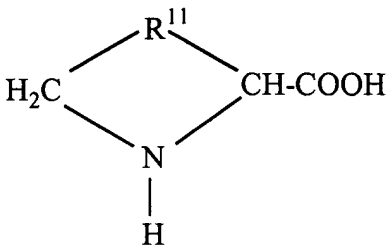
$aa^2$ is an imino acid having from 4 to 6 ring members;

$R^9$ is a straight chain alkyl group interrupted by one or more ether linkages and in which the total number of oxygen and carbon atoms is from 3 to 6, or is $-(CH_2)_m$-W where m is from 2 to 5 and W is –OH or halogen.

Claim 13 (original): The salt of claim 12 wherein $aa^1$ is selected from Phe, Dpa and wholly or partially hydrogenated analogues thereof.

Claim 14 (original): The salt of claim 13 wherein $aa^1$ is of R-configuration.

Claim 15 (currently amended): The salt of claim 12 wherein $aa^2$ is a residue of an imino acid of formula (V)



(V),

where $R^{11}$ is $-CH_2-$, $-CH_2-CH_2-$, $-S-CH_2-$, $-S-C(CH_3)_2-$ or $-CH_2-CH_2-CH_2-$, and, when the formula ~~(IV)~~ (V) ring is 5- or 6- membered, the formula ~~(IV)~~ (V) ring is unsubstituted or is substituted at one or more $-CH_2-$ groups by from 1 to 3 $C_1$-$C_3$ alkyl groups.

Claim 16 (original): The salt of claim 15 wherein $aa^2$ is of S-configuration.

Claim 17 (original): The salt of claim 12, wherein $aa^1$-$aa^2$ is (R)-Phe-(S)-Pro and the fragment -NH-CH($R^1$)–$B(OH)_2$ is of R-configuration.

Claim 18 (currently amended): The salt of claim 13 wherein the boronic acid is of formula (IX):

~~X-(R)-Phe-(S)-Pro-(R)-Mpg-B(OH)$_2$ (IX),~~

X-(R)-Phe-(S)-Pro-(R)-boroMpg-OH (IX),

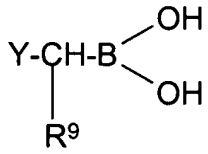
wherein X is $R^6$-$(CH_2)_p$-C(O)-, $R^6$-$(CH_2)_p$-$S(O)_2$-, $R^6$-$(CH_2)_p$-NH-C(O)- or $R^6$-$(CH_2)_p$-O-C(O)- wherein p is 0, 1, 2, 3, 4, 5 or 6 and $R^6$ is H or a 5 to 13-membered cyclic group which is unsubstituted or substituted by 1, 2 or 3 substituents selected from halogen; amino; nitro; hydroxy; a $C_5$-$C_6$ cyclic group; $C_1$-$C_4$ alkyl and $C_1$-$C_4$ alkyl containing, or linked to the cyclic group through, an in-chain O atom, the aforesaid alkyl groups optionally being substituted by a substituent selected from halogen, amino, nitro, hydroxy and a $C_5$-$C_6$ cyclic group~~.~~ ; and boroMpg-OH is a residue of an aminoboronic acid of the formula $H_2N$-CH($(CH_2)_3OMe$)$B(OH)_2$.

Claim 19 (original): The salt of claim 12 which comprises a divalent metal salt of the peptide boronic acid.

Claim 20 (original): A pharmaceutical formulation adapted for oral administration which comprises a salt of claim 1.

Claim 21 (currently amended): The salt of claim 1 wherein the organoboronic acid is of formula (III) below when included in a pharmaceutical formulation adapted for oral administration and comprising

a) a first species selected from a boronic acid of formula (III), ~~and~~ or said boronic acid when in the form of boronate ions thereof, or equilibrium forms of said boronic acid and of said boronate ions, ~~and~~ or combinations thereof:




(III)

wherein

Y comprises a moiety which, together with the aminoboronic acid residue -NHCH($R^9$)-$B(OH)_2$, has affinity for the substrate binding site of thrombin; and

$R^9$ is a straight chain alkyl group interrupted by one or more ether linkages and in which the total number of oxygen and carbon atoms is 3, 4, 5 or 6 or $R^9$ is $-(CH_2)_m$-W where m is from 2, 3, 4 or 5 and W is –OH or halogen; and

(b) a second species selected from multivalent metal ions having a valency n,

wherein the formulation has an observed stoichiometry of first to second species essentially consistent with a notional stoichiometry of n:1.

Claim 22 (withdrawn): A method of inhibiting thrombin in the prophylaxis or therapy of disease, comprising parenterally administering to a mammal suffering from, or at risk of suffering from, thrombosis a therapeutically effective amount of the salt defined in claim 1.

Claim 23 (canceled)

Claim 24 (withdrawn - currently amended): A medicament adapted for oral administration and comprising a therapeutically effective amount of a ~~multivalent metal~~ salt of ~~a boronic acid which is a selective thrombin inhibitor and has a neutral aminoboronic acid residue capable of binding to the thrombin S1 subsite linked through a peptide linkage to a hydrophobic moiety capable of binding to the thrombin S2 and S3 subsites, the salt comprising a cation having a valency n and having an observed stoichiometry consistent with a notional stoichiometry (boronic acid:cation) of n:1~~ claim 1.

Claim 25 (withdrawn): A medicament of claim 24 which is in solid dosage form.

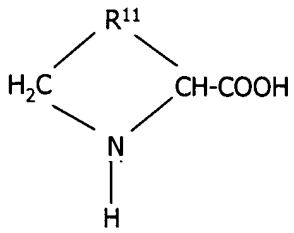
Claim 26 (withdrawn): A medicament of claim 25 wherein the boronic acid has a Ki for thrombin of about 100 nM or less.

Claim 27 (canceled).

Claim 28 (currently amended): The salt of claim 12, wherein:

$aa^1$ is selected from Phe, Dpa and wholly or partially hydrogenated analogues thereof;

$aa^2$ is a residue of an imino acid of formula (V);




(V)

where $R^{11}$ is $-CH_2-$, $-CH_2-CH_2-$, $-S-CH_2-$, $-S-C(CH_3)_2-$ or $-CH_2-CH_2-CH_2-$, and, when the formula ~~(IV)~~ (V) ring is 5- or 6- membered, the formula ~~(IV)~~ (V) ring is unsubstituted or is substituted at one or more $-CH_2-$ groups by from 1 to 3 $C_1$-$C_3$ alkyl groups;

$R^9$ is a straight chain alkyl group interrupted by one or more ether linkages and in which the total number of oxygen and carbon atoms is from 3 to 6.

Claim 29 (previously presented): The salt of claim 28 wherein $aa^1$ is of (R)-configuration, $aa^2$ is of (S)-configuration, and chiral centre $-NH-CH(R^9)-B(OH)_2$ is of (R)-configuration.

Claim 30 (previously presented): The salt of claim 29 wherein $R^9$ is alkoxyalkyl containing 4 carbon atoms, $aa^1$ is Phe or a wholly or partially hydrogenated analogue thereof, and $aa^2$ is azetidine-2-carboxylic acid or proline.

Claim 31 (previously presented): The salt of claim 30 wherein $R^9$ is 3-methoxypropyl.

Claim 32 (previously presented): The salt of claim 29 wherein the multivalent metal is calcium, magnesium or zinc.

Claim 33 (previously presented): The salt of claim 30 which is a hemicalcium, hemimagnesium or hemizinc salt.

Claim 34 (previously presented): The salt of claim 31 which is a hemicalcium salt.

Claim 35 (previously presented): The salt of claim 18 wherein X is $R^6$-$(CH_2)_p$-O-C(O)-, where $R^6$ is 5 to 13-membered aromatic or heteroaromatic group and p is 0 or 1.

Claim 36 (previously presented): The salt of claim 1 wherein the boronic acid is of the formula:
Cbz-(R)-Phe-(S)-Pro-(R)-Mpg-$B(OH)_2$.

Claim 37 (previously presented): The salt of claim 36 wherein the multivalent metal is calcium, magnesium or zinc.

Claim 38 (previously presented): The salt of claim 36 which is a hemicalcium salt.

Claim 39 (previously presented): The salt of claim 4 wherein $R^9$ is 3-methoxypropyl and the carbon atom to which $R^9$ is bonded comprises a chiral centre of (R)-configuration.

Claim 40 (currently amended): The salt of claim 39 which ~~is~~ consists essentially of a hemicalcium, hemimagnesium or hemizinc salt.

Claim 41 (new): The salt of claim 39 which comprises a hemicalcium or hemimagnesium salt.

Claim 42 (new): The salt of claim 36 which comprises a hemicalcium or hemimagnesium salt and which comprises anhydride species of the acid.

Claim 43 (new): The salt of claim 1 which comprises the boronic acid in anhydride form.

Claim 44 (new): The salt of claim 11 which comprises the boronic acid in the form of an anhydride.

Claim 45 (new): The salt of claim 21 wherein the first species comprises the organoboronic acid in the form of an anhydride.

Claim 46 (new): The salt of claim 38 which comprises the boronic acid in the form of an anhydride.

Claim 47 (new): The pharmaceutical formulation of claim 20 wherein the formulation is in the form of a tablet or a capsule.

Claim 48 (new): The pharmaceutical formulation of claim 47 wherein the tablet or capsule is enterically coated.

Claim 49 (new): The pharmaceutical formulation of claim 47 wherein the tablet or capsule is not enterically coated.

Claim 50 (new): The pharmaceutical formulation of claim 20 further comprising at least one further pharmaceutically active agent in addition to the salt of claim 1.

Claim 51 (new): The pharmaceutical formulation of claim 50 wherein the further pharmaceutically active agent comprises a cardiovascular treatment agent.

Claim 52 (new): A pharmaceutical formulation adapted for oral administration which comprises at least one salt of claim 11.

Claim 53 (new): A pharmaceutical formulation adapted for oral administration which comprises at least one salt of claim 39.

Claim 54 (new): The pharmaceutical formulation of claim 53 wherein the salt comprises the boronic acid in anhydride form.

Claim 55 (new): The pharmaceutical formulation of claim 54 wherein said at least one salt consists essentially of a single said metal and a single said boronic acid, the metal being selected from calcium and magnesium.

Claim 56 (new): The pharmaceutical formulation of claim 53 wherein the formulation is in the form of a tablet that is not enterically coated or a capsule that is not enterically coated.

Claim 57 (new): A pharmaceutical formulation adapted for oral administration which comprises as an active agent a salt of claim 36.

Claim 58 (new): The pharmaceutical formulation of claim 57 wherein the salt is selected from the hemicalcium and hemimagnesium salts of a boronic acid of the formula Cbz-(R)-Phe-(S)-Pro-(R)-boroMpg-OH;

wherein boroMpg-OH is a residue of an aminoboronic acid of the formula $H_2N$-$CH((CH_2)_3OMe)B(OH)_2$.

Claim 59 (new): The pharmaceutical formulation of claim 58 wherein the active agent is the hemicalcium salt.

Claim 60 (new): The pharmaceutical formulation of claim 59 wherein the salt comprises the boronic acid in anhydride form.

Claim 61 (new): The pharmaceutical formulation of claim 59 which is in the form of an enterically coated tablet or capsule.

Claim 62 (new): The pharmaceutical formulation of claim 59 which is in the form of a tablet or capsule which is not enterically coated.

Claim 63 (new): A method of inhibiting thrombin in the prophylaxis or therapy of disease, comprising orally administering to a mammal suffering from, or at risk of suffering from, thrombosis a therapeutically effective amount of the salt of claim 1.

Claim 64 (new): A method of inhibiting thrombin in the prophylaxis or therapy of disease, comprising orally administering to a mammal suffering from, or at risk of suffering from, thrombosis a therapeutically effective amount of the salt of claim 11.

Claim 65 (new): A method of inhibiting thrombin in the prophylaxis or therapy of disease, comprising orally administering to a mammal suffering from, or at risk of suffering from, thrombosis a therapeutically effective amount of the salt of claim 36.

Claim 66 (new): A method of inhibiting thrombin in the prophylaxis or therapy of disease, comprising orally administering to a mammal suffering from, or at risk of suffering from, thrombosis a therapeutically effective amount of the pharmaceutical formulation of claim 58.

Claim 67 (new): A method of inhibiting thrombin in the prophylaxis or therapy of disease, comprising orally administering to a mammal suffering from, or at risk of suffering from, thrombosis a therapeutically effective amount of the pharmaceutical formulation of claim 59.

Claim 68 (new): A method of inhibiting thrombin in the prophylaxis or therapy of disease, comprising orally administering to a mammal suffering from, or at risk of suffering from, thrombosis a therapeutically effective amount of the pharmaceutical formulation of claim 60.

Claim 69 (new): A method of inhibiting thrombin in the prophylaxis or therapy of disease, comprising orally administering to a mammal suffering from, or at risk of suffering from, thrombosis a therapeutically effective amount of the pharmaceutical formulation of claim 61.

Claim 70 (new): A method of inhibiting thrombin in the prophylaxis or therapy of disease, comprising orally administering to a mammal suffering from, or at risk of suffering

from, thrombosis a therapeutically effective amount of the pharmaceutical formulation of claim 62.

Claim 71 (new): The method of claim 66 wherein the salt is in solid dosage form.

Claim 72 (new): The method of claim 67 wherein the salt is in solid dosage form and comprises the boronic acid in anhydride form.

Claim 73 (new): The salt of claim 1 wherein the salt comprises anhydride species.

Claim 74 (new): The salt of claim 11 wherein the salt comprises anhydride species.

Claim 75 (new): The salt of claim 38 wherein the salt comprises anhydride species.

Claim 76 (new): The salt of claim 1 which is substantially anhydride-free.

Claim 77 (new): The salt of claim 11 which is substantially anhydride-free.

Claim 78 (new): The salt of claim 38 which is substantially anhydride-free.

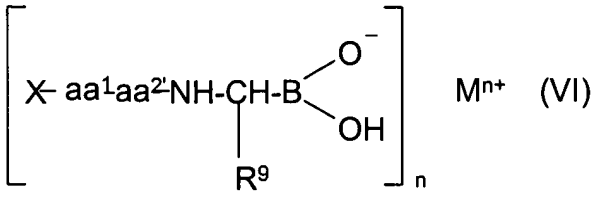
Claim 79 (new): The pharmaceutical formulation of claim 20 wherein the salt is substantially anhydride-free.

Claim 80 (new): The method of claim 66 wherein the salt is substantially anhydride-free.

Claim 81 (new): The salt of claim 1 wherein the salt comprises an acid salt in which both B-OH groups of formula (I), when trigonally represented, are deprotonated.

Claim 82 (new): The pharmaceutical formulation of claim 20 which comprises a mixture of multivalent metals.

Claim 83 (new): The salt of claim 12 wherein the salt is of formula (VI)




where $M^{n+}$ is a divalent or trivalent metal cation, and n is 2 or 3, and the trigonally represented boronyl group – $B(O^-)(OH)$ may comprise tetrahedral species.

Claim 84 (new): The salt of claim 83 wherein $M^{n+}$ is $Ca^{2+}$.

Claim 85 (new): A pharmaceutical formulation adapted for oral administration which comprises at least one salt of claim 83.

Claim 86 (new): The pharmaceutical formulation of claim 85 which comprises a mixture of cations.

Claim 87 (new): The salt of claim 1 wherein the organoboronic acid is of the formula Cbz-(R)-Phe-(S)-Pro-(R)-boroMpg-OH, wherein boroMpg-OH is a residue of an aminoboronic acid of the formula $H_2N$-CH($(CH_2)_3$OMe)$B(OH)_2$, and is included in a pharmaceutical formulation adapted for oral administration, the salt comprising

a) a first species selected from (i) said boronic acid or (ii) said boronic acid when in the form of boronate ions thereof, or equilibrium forms of said boronic acid and of said boronate ions, or combinations thereof; and

(b) a second species selected from multivalent metal ions.

Claim 88 (new): The salt of claim 87 wherein the pharmaceutical formulation further comprises one or more additional components selected from a) fillers or extenders; b) binders; c)

humectants; d) disintegrating agents; e) solution retarding agents; f) absorption accelerators; g) wetting agents; h) absorbents; i) lubricants; and j) dissolution aids, or mixtures thereof.

Claim 89 (new): The pharmaceutical formulation of claim 55 wherein the metal is calcium.

Claim 90 (new): A composition of matter comprising the salt of claim 1 wherein the organoboronic acid is of the formula Cbz-(R)-Phe-(S)-Pro-(R)-boroMpg-OH, wherein boroMpg-OH is a residue of an aminoboronic acid of the formula $H_2N$-CH(($CH_2$)$_3$OMe)B(OH)$_2$, the salt consisting essentially of:

a) a first species selected from (i) said boronic acid or (ii) said boronic acid when in the form of boronate ions thereof, or equilibrium forms of said boronic acid and of said boronate ions, or combinations thereof; and

(b) a second species selected from calcium and magnesium ions,

the composition of matter optionally further comprising one or more additional components selected from at least one pharmaceutically acceptable, orally suitable adjuvant, diluent or carrier; and at least one cardiovascular treatment agent.

Claim 91 (new): The composition of claim 90 wherein the second species is calcium ions and the first species comprises boronate species having the characteristics of boronate species derived at least from a molecule of the boronic acid which has been singly deprotonated.

Claim 92 (new): The composition of claim 90 wherein the second species is magnesium ions and the first species comprises boronate species having the characteristics of boronate species derived at least from a molecule of the boronic acid which has been singly deprotonated.

Claim 93 (new): The composition of claim 91 which is adapted for oral administration.

Claim 94 (new): A method for making a salt of claim 12, comprising:

combining in a solvent diethanolamine and an ester of a boronic acid as defined in claim 12;

allowing or causing a precipitate to form and recovering the precipitate;

converting the precipitated material into the free organoboronic acid by contacting the precipitated material with an aqueous acid or base; and

reacting the organoboronic acid with a base of a pharmaceutically acceptable multivalent metal to form to a salt as defined in claim 12.